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Economic and Technological Drivers of Generic Sterile Injectable Drug Shortages

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Over the past few years, an increasing number of critically needed medicines have been in short supply. Using economic theory to frame the drug-shortage problem, this paper explores why and how manufacturing-quality problems could combine with other economic and technological factors to result in shortages of generic sterile injectable drugs. The fundamental problem we identify is the inability of the market to observe and reward quality. This lack of reward for quality can reinforce price competition and encourage manufacturers to keep costs down by minimizing quality investments. The US Food and Drug Administration's (FDA's) need to use its regulatory flexibility, on behalf of patients, to avoid shortages of medically necessary drugs may further strengthen the incentive to "push the envelope" on quality. These dynamics may have produced a market situation in which quality problems have become sufficiently common and severe to result in drug shortages.

In December 2009, the FDA sent inspectors to a sterile-injectable facility following a propofol recall issued by the manufacturer. The FDA's investigation confirmed the manufacturer's earlier finding that the product had high levels of endotoxin, which can cause fever and shock. Previously another major manufacturer had recalled multiple batches of propofol for particulate contamination. By early 2010, both companies had decided to halt production of propofol, leaving only one company to meet the market demand. With the remaining firm unable to sufficiently ramp up production and inventories running out, a drug shortage occurred.[1]

Variations on this disconcerting scenario have been playing out with an increasing frequency over the past few years. In 2011, drug shortages rose to unprecedented levels, with 251 medically necessary drugs affected. Seventy-three percent of these drugs were sterile-injectable products such as the anesthetic propofol, injectable morphine, epinephrine used in cardiac arrest and anaphylactic shock, intravenous nutritional supplements, and chemotherapy agents. The resulting health crisis has been particularly pronounced because these drugs are medically necessary, meaning that they are used to treat or prevent a serious disease or medical condition and that there is no appropriate substitute.

This article focuses on generic sterile injectables because these drugs constitute the lion's share of current drug shortages. Using economic theory to evaluate incentives, we explore why and how manufacturing-quality problems may combine with other economic and technological factors to result in shortages of generic sterile injectable drugs. A fundamental problem we identify is that the market does not sufficiently recognize or reward quality. An important, but largely unrecognized aspect of quality is the ability to reliably meet customer demand. Although today's buyers may now be more aware of quality problems with sterile injectables, buyers appear to generally discount quality concerns and to focus principally on obtaining the lowest prices possible. This behavior is likely based on a belief that all marketed products are of equivalent quality. The resulting lack of reward for quality may encourage manufacturers to keep costs down by, for example, minimizing quality-related investments in areas such as maintenance of production facilities and equipment, quality control testing and oversight, and timely response to early indicators of quality problems. In the case of sterile injectables, there is very little margin for error, so a lack of sustained investment in infrastructure and vigilant quality focus can produce what economists term a "bad market equilibrium," particularly the problem of reliability, in which quality problems are rife.

LINK BETWEEN MANUFACTURING QUALITY AND SHORTAGES

Not every production disruption turns into a shortage, but virtually all shortages are preceded by disruptions in production. Sometimes supply disruptions are unanticipated by the manufacturer, as a result of natural disasters or unforeseeable

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Received 3 October 2012; accepted 29 October 2012; advance online publication 23 January 2013. doi:10.1038/clpt.2012.220

disruptions in the supply of the active pharmaceutical ingredient. Although such unanticipated events have the potential to cause major shortages, very few actual shortages are linked to such unanticipated events.

Instead, drug shortages are first and foremost driven by the inability of various firms to maintain production because of the failure of quality management in facilities that produce the finished dosage form of the drug (rather than the active ingredient). As **Figure 1** indicates, these failures were directly responsible for 56% of sterile injectable drug shortages in 2011.

Many other shortages not formally considered as related to manufacturing quality problems have in fact their origins in this issue. Some shortages caused by delays and capacity issues are driven by quality-related shutdowns. In some other cases, shortages resulting from manufacturing failures for one drug increased demand for another drug by so much that companies producing it were not able to catch up with demand. In this case, quality-based shortages of one drug lead to shortages of another drug (up to 7% of sterile-injectable shortages).

Some firms have discontinued older, medically necessary products. Product discontinuations, which accounted for 9% of sterile-injectable shortages in 2011, are often triggered by capacity constraints, many of them brought about by quality-related production line disruptions. Economic theory suggests that companies would generally consider a product to be worth producing if the revenue it generates can cover the costs of production. This production rule no longer holds true when the firm reaches production capacity and managers are forced to make trade-offs among products, exposing products with low–average revenue for potential cuts as companies try to optimize profitability of their production lineup. Such pressures could be contributing to the discontinuations we observe.

When drugs are discontinued with little or no notice, the health-care system and its patients may experience unexpected supply shortfalls of critical drugs. In addition, given the time required to increase production at an existing line, initiate a new site, or (the most challenging) bring on a new manufacturer, shortages may occur even with advance notice of discontinuation. This is why in concert with President Obama's Executive Order no. 13,588, the Agency took steps in late 2011 to encourage manufacturers to notify FDA of potential shortage situations. Congress subsequently embodied that recommendation in law when it passed the Food and Drug Administration Safety and Innovation Act.

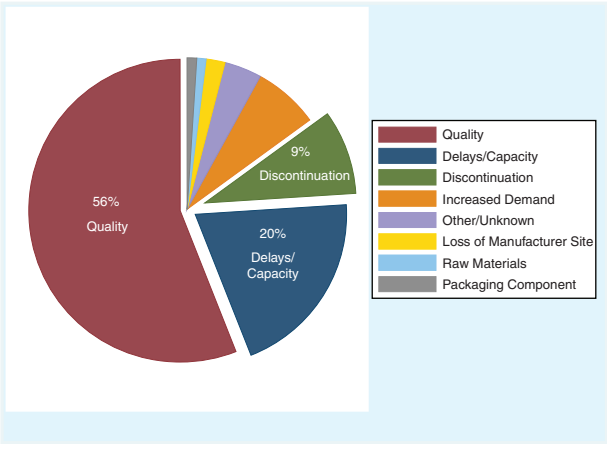

Figure 1 Reported reasons for sterile injectable drug shortages in 2011.

Manufacturers have the responsibility to establish appropriate manufacturing practices and conditions at sterile-injectable facilities and to ensure that they are sufficiently robust to prevent hazardous situations. Ensuring their robustness is in many ways more complex than for non-sterile products. Management's daily decisions on myriad issues involving equipment, materials, maintenance, staff qualifications, supervision, process control, and investigations of any problem can significantly impact sterility assurance. The primary mode of sterile injectable production, aseptic processing, is not a forgiving process so any such variable, if not properly attended to, can lead to contamination.

The current shortage crisis with generic sterile injectable drugs follows directly from contamination problems at multiple facilities—problems that have required correction through upgrades of systems and/or production processes. The problems leading to shortages have included detection of shards of glass and metal in vials as well as of bacteria, endotoxin, or mold in what are supposed to be sterile products.[2] These problems have differing etiologies some can be linked to insufficient maintenance of production facilities and equipment; some are a result of antiquated/inadequate aseptic operation design; and others stem from suboptimal quality control testing and oversight and lack of timely responses to indicators of quality problems. The scope of these problems and the resulting remediation needs have varied across firms. In some cases, the widespread and systemic nature of the manufacturing failures has led firms to shut down all production while they address the problems. In most cases, firms have been able to continue production while improvements were being made, although often at a reduced rate.

ECONOMIC INCENTIVE TO MINIMIZE INVESTMENT IN MANUFACTURING QUALITY

The drivers behind the quality problems we describe above are multifaceted, but we postulate that at their core is the failure of the market to sufficiently reward quality.

Market does not reward quality

We postulate that at the heart of the quality problem is the fact that generic manufacturers compete on price. Intense price competition is a reflection of the generic drug framework—that is, generic versions of the same drug are designed to have the same efficacy and side-effect profiles. Buyers—in this case, hospitals and clinics—consider any given generic products as perfect substitutes, giving manufacturers little room for differentiation. Therefore, buyers have not been attuned to differences in the quality of production. In their minds, the products are of sufficient quality if they are on the market. The lack of reliability of supply stemming from quality failures has not seemed to be a factor of concern, possibly because the US drug supply has generally been reliable and of high quality in recent decades.

Another reason for lack of awareness of quality differences results from providers' inability to accurately assess production quality for a given drug. Providers are more likely to suspect a causal link and therefore report an adverse event if a drug is used in a relatively healthy patient population. But, generally, injection and infusion drugs are administered to patients who have compromised immune systems and little ability to fight infections and/or other comorbidities. Few health-care providers consider whether substandard manufacturing could be the source of an adverse event, both because of the general high quality of the US drug supply, in which product defects are quite rare, or because certain adverse events, such as infection, are common in the treated population. As such, the propofol example cited in the introduction is more an exception than the rule. In that case, providers were able to establish a potential causal link because the drug is often administered to relatively healthy patients.[1]

FDA experience suggests that firms responses to price competition vary. Despite buyers' unwillingness to pay a premium for quality, many firms strive to exceed minimum manufacturing standards. Nonetheless, economic incentives create pressures on firms to minimize expenditures and thus generate a conflict between patient safety and profit.

Quality is not fully transparent

A drug manufacturer is responsible for implementing dependable daily operations that assure consistent drug quality. Management's daily decisions on myriad issues involving equipment, materials, maintenance, staff qualifications, supervision, process control, and investigations will ultimately determine the quality of the drugs that are shipped from a given facility.

The FDA assesses whether a facility is in a state of control through periodic inspections that provide an evaluation of a firm's manufacturing operations, including their system for quality management. Almost all major sterile-injectable manufacturing facilities producing for the US market are inspected at least every 2 years, because they are based domestically. Between inspections, the FDA relies, in part, on firms to be forthcoming about their quality problems, which they report by issuing defect reports (Field Alert Reports and Biological Product Defect Reports).

Defects in sterile injectable products can be difficult to detect because microbial contamination may be non-uniform and episodic. This lack of uniformity can confound conventional sampling plans. In addition, microbial contamination can increase after production, which means that more sensitive testing must be done at production time. For these reasons, the FDA has made attempts over the last few years to enhance its audit of a site's state of control and quality problems by developing a cadre of highly trained and experienced inspectors to conduct inspections of complex facilities such as those that produce sterile injectables.

Exercising regulatory flexibility to avert shortages may have unintended consequences

If the FDA uncovers signals of emerging problems, it seeks the firm's cooperation in voluntarily correcting the potentially major issue before there is an impact on product quality. The agency will weigh the benefits and downsides when taking regulatory action. The benefits are not only the immediate prevention of adverse health outcomes but also the long-term incentives for firms to keep all of their facilities and processing lines up to quality standards. On the other hand, addressing developing quality problems that have the potential to pose health risks may require slowing down or temporarily disrupting production. When these disruptions have the potential to affect medically necessary products, the agency must balance the harm from loss of access to the product with the potential impact of a manufacturing problem. In some cases where shortages are already occuring, FDA has sometimes agreed to special provisions that permit continued distribution of the medically necessary drugs. For example, the FDA allowed for distribution of one product containing glass particles if accompanied by a letter instructing health-care professionals to use a filter to remove the particles. In another case, the FDA allowed distribution of a product containing crystals, and the providers were directed to dissolve the crystals by warming the vials.

The FDA's need to use regulatory flexibility on behalf of patients to avert and mitigate shortages could have unintended long-term consequences when coupled with the market's lack of reward for quality. Economic models predict that, in the face of the seeming intertemporal inconsistency created by dual FDA objectives, quality investments would be lower than if the FDA could use preemptive enforcement without regard for disruptions in medically necessary products. This dynamic may further reinforce the economic incentives to minimize quality investments given the nature of competition (based on price, not quality).

FACTORS REINFORCING INSUFFICIENT QUALITY INVESTMENTS

The situation we describe above is a steady characteristic of medically necessary generic drug markets. The market's lack of recognition of quality differences in generic sterile injectable products can influence firms to adopt a reactive approach to quality management. In such cases, a firm might wait until

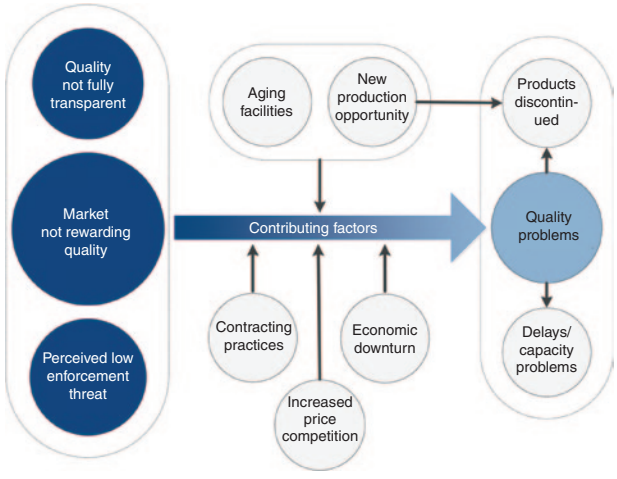

Figure 2 Economic drivers of manufacturing quality problems.

problems are identified before taking action, in contrast to taking a proactive and vigilant approach that is necessary to sustain a dependable operation. When dealing with such a reactive quality-management approach, the medically necessary status of certain sterile injectable drugs impels the FDA to consider the medical ramifications of lack of access. This in turn may give short-sighted firms an incentive to manufacture under a minimum level of control. This outcome is predicted by economic theory, which stipulates that rational agents (be they firms or individuals) will make a cost–benefit analysis when engaging or perhaps disengaging in a particular behavior.

In addition to the key drivers mentioned above, several other factors may have further exacerbated insufficient quality investments: aging facilities, new production opportunities, contracting practices, economic downturn, and a possible increase in price competition. **Figure 2** shows how these factors interact with one another in the context of drug shortages.

Aging facilities

In contrast to the production of tablets, facilities producing generic sterile injectables are primarily based in the United States because of high transportation costs associated with liquids that often require climate control. New manufacturing lines have been added by various manufacturers over the past decade, but some primary production lines and facilities are quite old. A review of inspection reports for key facilities suggests that some facilities at the heart of current drug shortages have been in operation continually since the 1960s. The reports suggest that certain manufacturing lines have undergone only limited upgrades during that time while running 24 hours a day, 7 days per week, a finding consistent with a 2011 report.[3]

Such aging facilities require upgrades, but low margins may make the economics of such investments unattractive. Although contemporary facilities are highly automated and use isolators and other separation technologies to protect the processing line from contamination risks, older facilities typically include processing lines and facility layouts that are less effective at mitigating the various operational variables that pose risks to product sterility. If the equipment is not well designed or is poorly maintained, repeated or extensive manual interventions often occur due to mechanical problems. When production line operators perform manual activities near an insufficiently protected product, they raise the risk of microbial contamination.[4] Inadequately maintained or designed equipment has also resulted in particles being shed into the product, including metal or glass shavings.[2]

New production opportunities

Magnifying the problem of aging facilities, firms have been adding many new products to their portfolios.[3] Even before the drug-shortage crisis, generic sterile injectable lines were generally operating at full capacity. This means that without further expansion in capacity, new marketing opportunities would force firms to make trade-offs between which products to produce and at what volume.[3] In addition, line operators need to turn over lines between products more frequently if those new products are added rather than replacing what is in the current production lineup. This line turnover can additionally introduce opportunities for sterility problems that can compromise product quality, especially if it involves production lines that are not fully automated.

Contracting practices

Not only are buyers unable to observe manufacturing quality, but firms that contract out manufacturing of their product often do not have the same level of insight into or oversight of the contract manufacturer's quality systems as they would have into their own. Overcommitment on manufacturing capacity by a contract manufacturer can lead to an unsustainably high number of products on each line and substandard oversight of the process. Contracted products are primarily branded sterile injectable products marketed by emerging companies without their own production facilities. Their manufacturing is then contracted not to large branded manufacturers but to firms that primarily produce and market many generic products. These relationships are proprietary, so buyers and their representatives generally have no knowledge that a drug they are buying may be made by a contract manufacturer.

Failure-to-supply clauses are another contracting-related issue worth mentioning. Such failure-to-supply clauses are commonly used in contracts between manufacturers and their buyers or buyers' representatives. Contracts generally place a penalty for failure to supply a product, but that penalty is structured as a difference between the contracted rate and the rate that a provider had to pay for an alternative source. Drug shortages have generally not triggered these clauses because there often is no alternative source.[3] Therefore, these clauses have not worked as intended to create an incentive for firms to avoid supply problems.

Economic downturn

The recession may have additionally increased pressure on manufacturers to cut cost. Employment in pharmaceutical manufacturing as a whole was hard hit during the recession, with the number of pharmaceutical manufacturing jobs shrinking by 15% from December 2007 to June 2009.[5] Cost cutting appears to have become, at least for the time being, a strategic focus of pharmaceutical companies. The workforce reductions within the pharmaceutical manufacturing industry, which had been occurring before the recession, accelerated during the downturn both through layoffs and voluntary attrition. Some companies made direct cuts to their manufacturing and quality control operations.[6] The threat of looming job cuts may have caused at least some of the best-qualified employees to leave and find employment elsewhere, leaving behind less-qualified workers.[7] Manufacturers of sterile injectables appear not to have been immune to cost-cutting initiatives.[8]

Increased price competition

Some have argued that the Medicare Modernization Act of 2005 (MMA) had an adverse impact on profit margins for generic sterile injectable drugs after it sharply lowered reimbursement rates that providers receive for provider-administered sterile injectables and other Part B drugs.[9,10] This reimbursement was

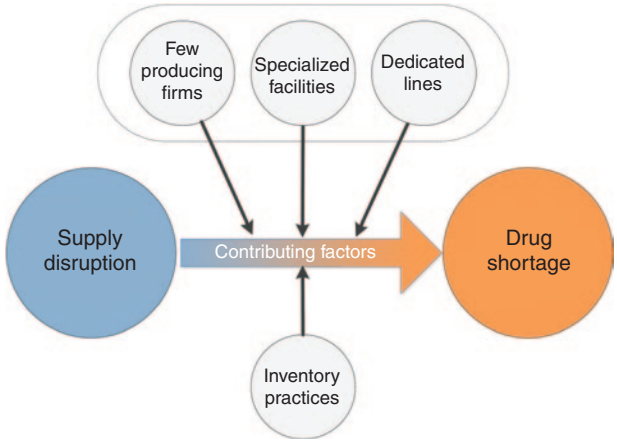

Figure 3 Factors that turn a supply disruption into a shortage.

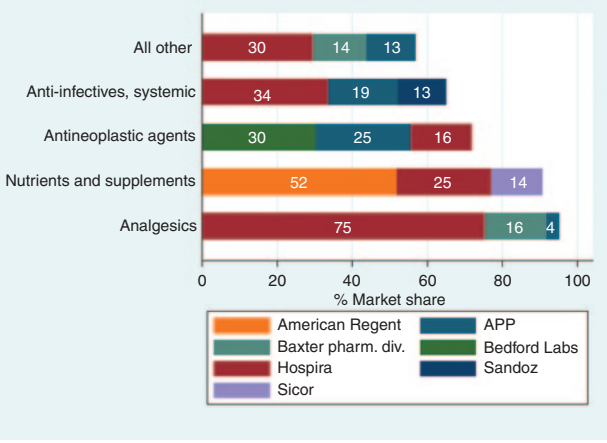

Figure 4 Market concentration in select generic sterile-injectable classes. Information from IMS Health, National Sales Perspective™.

set by the MMA at 106% of the average selling price, which is roughly the average of actual transaction prices paid by providers for any version of a given molecule. Some have postulated that lower reimbursement to providers in turn put more price pressure on generic manufacturers. However, trends in shortages of drugs affected by the payment reform are similar to the pattern among drugs that should not have been affected by it.[11] In addition, many industry observers have told us that price competition had been a feature of the sterile-injectable industry long before the MMA—something that is consistent with the dynamics we have discussed in the previous section.

Empirically determining to what extent the law contributed to the crisis beyond what we have already discussed is difficult, primarily because of lack of price transparency data before 2005. For this reason, we were unable to confirm any of the opposing positions.

WHY DO SUPPLY DISRUPTIONS TURN INTO SHORTAGES?

We have explained the role that manufacturing problems have played in supply disruptions. In this section, we explain why temporarily or permanently halting production on even a single production line so frequently results in a market-wide drug shortage. We summarize these factors in **Figure 3**: high market concentration, the need for specialized facilities and dedicated lines, and the practice by distributors and health-care providers of holding relatively low levels of inventory.

High market concentration

A key factor that helps turn a single production line disruption into a drug shortage is high market concentration. Seven firms make up virtually all of sterile-injectable production as measured in standard units.[12] As one narrows the analysis down to specific drug classes, the concentration further increases. **Figure 4** shows a conservative view of market concentration in selected drug classes (conservative because it underestimates the market share of manufacturers who produce drugs for other companies). Concentration further increases if one drills down to finer market definitions, e.g., specific molecules. For example, in 2008, Teva held a 68% market share of bleomycin, whereas Bedford Laboratories held a 62% share of cytarabine.[12]

Specialized facilities and dedicated lines

One key reason for the high market concentration is that sterile injectable products must be produced in highly specialized facilities. Production must take place in a "clean room" environment with well-defined manufacturing processes and controls to assure that they are sterile, meaning free of contamination from all microorganisms and essentially free of visible particulate matter.[13]

Not only must drugs be produced in specialized facilities, but their production is often committed to specific production lines within those facilities because of the drugs' chemical properties, presentation form, and potential for cross-contamination.[14] Most drugs' chemistry requires that they be produced using a complex process of aseptic processing, in which the drug product, container, and closure are subject to sterilization separately and then brought together. A smaller number of drugs need only undergo terminal sterilization, in which the product in its final container is subject to a sterilization process through heat or radiation. For some, the sterilized product further requires an additional lyophilization step in which water from the solution is removed in a highly controlled environment under high vacuum and extreme cold temperatures to yield a powder. Apart from the differences in production process, certain drug classes such as cephalosporins, penicillins (antibiotics), and some cytotoxics (oncology) require dedicated equipment, and sometimes even dedicated buildings, which then cannot be used to produce other types of drugs. Finally, manufacturing equipment, due to compatibility issues, may be capable of filling containers of only certain limited size ranges (e.g., different equipment may be needed for a 1- vs. 25-ml vial size) and container types (vials vs. syringes). This further restricts products to specific lines.

Despite the limited fungibility of production driven by dedicated production lines, generic manufacturers do not appear to arrange for backup facilities. Our analysis of sterile-injectable applications approved between 2000 and 2011 identified close to 900 approved abbreviated new drug applications (ANDAs). Of those, only 11, or just over 1%, referenced more than one facility for production of the finished drug. This contrasts with branded sterile-injectable applications, almost 20% of which

were approved with backup facilities during the same time period. About 5–6% of the studied sterile-injectable ANDAs have subsequently submitted additional production sites. Those submissions occurred on average 4 years after original submission. In our study window, no sterile-injectable ANDA submitted additional sites within 1 year of original application.

Because a specific set of products is often committed to select production lines, a process disruption on these lines, especially if they are few, can readily turn into market-wide drug shortages for a whole group of products. Such coproduction of drugs is the reason that drug shortages have "traveled" across therapeutic classes.[3] For example, after one key facility with cytotoxic lines shut down in early 2010, the number of shortages of chemotherapy drugs increased from 4 to 24 (ref. 15).

Inventory practices

Generally low inventory levels further increase the risk that a supply disruption will turn into a drug shortage.[16] Such inventory practices reduce expenses by eliminating surplus production and inventory holding costs but increase the risk that even a modest disruption in supply will result in shortage. These low inventory levels are one reason that notifying the FDA early about supply disruptions is important.

DISCUSSION

In this article, we illustrate the interaction of many factors contributing to shortages of generic sterile injectable drugs. Although we are unable to empirically validate many of the interactions due to data limitations, we base our explanation of the recent preponderance of generic sterile-injectable shortages on economic theory and corroborate it with the FDA's experience as well as conversations with various stakeholders.

We argue that the fundamental problem is insufficient market reward for quality (including reliability of production) stemming from the buyers' inability to observe it. This in turn gives manufacturers strong incentives to minimize quality system investments, especially when faced with pressures brought about by new production opportunities, aging facilities, and the recent economic downturn. Unfortunately, there is very little margin for error in the production of sterile injectables. As a result, quality problems caused by particulate and microbial contamination are more likely to take place. Manufacturers then feel compelled to remediate the problems because consequences of contamination can be dire. The necessary remediation efforts have slowed or stopped production of many drugs that subsequently went into shortage.

Our explanation for drug shortages is specific to generic sterile injectable products, so caution should be applied when extrapolating the conclusions of this article to other drug shortages. Besides the increased vulnerability of the production process and the serious consequences of sterile drug contamination, oral products are also less vulnerable to shortages because is much easier for a firm to ramp up production of oral solid and liquid drug products. Brand name have also contributed to serious drug shortages but they differ from generic injectables in important ways. Although the quality of branded sterile injectables is also difficult to observe and they face an equally, if not more, complex manufacturing environment, high margins earned by their products provide a countervailing incentive to prevent production disruptions. As a result, branded manufacturers have a greater incentive to invest in quality systems and to maintain spare capacity in case production unexpectedly has to be shut down. When production disruptions occur, they tend to be resolved faster.

The FDA is committed to finding new tools and approaches to prevent and resolve drug shortages. Some of those approaches—in particular, early notification—have already borne fruit. Elsewhere, Kweder and Dill elaborate on the many ways that the FDA has been working on preventing and mitigating shortages.[17]

However, we have now reached a point where FDA needs to engage the marketplace to help address the manufacturing problems, which unilateral FDA actions have not been able to prevent. FDA could support the buyers and payers in their purchase and reimbursement decisions by providing them with meaningful manufacturing quality metrics. This general approach has been successfully used in many other settings where quality is difficult to observe or quality signals are difficult to interpret. Restaurant grades, HMO scorecards or even a US Pharmacopeia stamp on vitamins are just a few among many tools that utilize this concept. It would then be up to the marketplace to answer the ultimate question: how much are we willing to pay for quality?

CONFLICT OF INTEREST

The authors declared no conflict of interest.

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